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Title of Grant: Predictive Multiscale Modeling of Microbial Consortia Biofilms

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Abstract Text

Chronic wounds are categorized as nonhealing wounds that do not proceed through resolution within a standard time period. Nonhealing, chronic wounds impact over eight million US patients and cost an estimated 30-60 billion USD in healthcare costs annually. Chronic wounds are challenging to treat because they are typically colonized by consortia growing as biofilms. *Pseudomonas aeruginosa* is an opportunistic pathogen commonly associated with chronic wounds, cystic fibrosis lungs and medical device-related infections. Microorganisms, including *P. aeruginosa*, maximize fitness by prioritizing catabolism of certain carbon sources while repressing catabolism of non-preferred carbon sources, a regulatory process known as carbon catabolite repression (CCR). CCR is one of the most important global regulatory systems and is central to nutrient acquisition for growth and cellular energy generation as well as for virulence associated processes. CCR strategies and regulatory networks of widely-studied microorganisms like *Escherichia coli* and *Bacillus subtilis* have become paradigms of substrate preference where glucose is catabolized prior to other sugars like lactose or organic acids like acetic acid. Many *Pseudomonads* including *Pseudomonas aeruginosa* have evolved a markedly different CCR-based selection of substrates. *Pseudomonads* prioritize the consumption of organic acids including acetic, citric and lactic acids over catabolism of glucose using a CCR strategy that has been termed 'reverse diauxie'.

Context: The presented study uses multi-omics to document reverse diauxie during both planktonic and biofilm growth of a *P. aeruginosa* strain isolated from a chronic wound. The *P. aeruginosa* data is integrated into a spatially and temporally resolved metabolic model for a three species (*P. aeruginosa, Staphylococcus aureus, Clostridium perfringens*) biofilm. The three species have largely complementary metabolisms exhibiting reverse diauxie, diauxie and an amino acid-based fermentation metabolism respectively which result in the emergent property of enhanced biomass productivity relative to the respective monocultures. The enhanced biomass productivity is a major medical challenge because it represents enhanced wound bioburden for the host. This study provides ecological and *in silico* insight into the biofilm consortia phenomena providing new opportunities to manipulate these communities including, potentially, new strategies for treating chronic wound infections.

Data: A combination of physiological, exometabolomics and label-free proteomics data quantified reverse diauxie in *P. aeruginosa* highlighting the expressed metabolic strategy even in the presence of stresses like mass transfer limitation of O_2.

Evaluation: The *P. aeruginosa* isolate is part of an *in vitro,* three species biofilm. The metabolism and omics data are being used to refinine a multiscale, spatially- and temporally-resolved metabolic model of a biofilm consortia. The model is being used for predicting microbial phenotypes, species distributions and species abundance in diverse environments including chronic wounds. Evaluation of model predictions is ongoing.

Limitations: Spatially resolved measurements of intraspecies metabolite exchanges within biofilms are difficult to achieve in order to verify some predictions.

Version control: Version controlling is linked to research publications. The appropriate model version and processing files are made available specific to a publication.

Documentation: All code is documented for readability and logic progression.

Dissemination: Code for models can be found at the MSM IMAG wiki website, PI websites, and as supplemental files in publications.

Independent reviews: We intend to develop and evaluate MATLAB and COBRA toolbox versions of our codes to test consistency across different implementation and to enhance distribution.

Test competing implementations: Competing implementations are being reviewed for metabolism representation and coverage.

Conform to standards: Code conforms to best practices adopted by the COBRA metabolic modeling community.